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## HIGH PERFORMANCE COMPUTING APPLICATIONS IN NEUROBIOLOGICAL RESEARCH

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### ABSTRACT

The human nervous system is a massively parallel processor of information. The vast numbers of neurons, synapses and circuits is daunting to those seeking to understand the neural basis of consciousness and intellect. Pervading obstacles are lack of knowledge of the detailed, three-dimensional (3-D) organization of even a simple neural system and the paucity of large scale, biologically relevant computer simulations. We use high performance graphics workstations and supercomputers to study the 3-D organization of gravity sensors as a prototypic architecture foreshadowing more complex systems. Scaled-down simulations run on a Silicon Graphics workstation and scaled-up, three-dimensional versions run on the Cray Y-MP and CM5 supercomputers.

### INTRODUCTION

It is with awe that humankind peers into the universe with ever more advanced computer technologies, discovering new worlds and breathtaking new information about stars and planets already familiar to us through the eyes of astronomers. We are on the verge of looking back through time to the beginning of the universe, thanks to new telescopes and our ability to put them into the rarefied environment of space. But what is more remarkable is that the first burst of energy that began the process of creation of the physical universe also defined the conditions that ultimately led to the evolution of life on our planet, Earth. A brain would evolve that could not only contemplate the beauty of the universe but also seek out the physical principles that govern it. Still, while we look outward with wonder and curiosity we often fail to look inward with the same sense of appreciation of the ultimate product of evolution, that inner universe that consists of billions of neurons and trillions of synapses - all within the few pounds that constitute a nervous system. There is no greater adventure before us than to understand the organization and functioning of this system; and advanced, high performance computers are essential to meet the challenges of this formidable task.

Knowledge of the complete functional organization of even a minute part of a sensory organ or of a cortical area still eludes us, even though that knowledge could contribute

greatly to our general understanding of the structural basis of normal neural functioning. The main obstacle is the huge volume of data that has to be collected, stored, manipulated and understood. Reconstructing a cubic millimeter of neural tissue at the ultrastructural level, for example, yields terabytes of data. Nevertheless, knowledge of the connectivities in such a small cube of neural tissue would provide insight into the basis of abnormal neural functioning and possibly improve the quality of life for many now afflicted with neural disorders. In addition, knowledge of how biological systems are organized to process, store, recall or forget, and synthesize information can lead to the development of more intelligent computers for applications on Earth and for use as smart devices in probes to distinguish what is new and exciting from what is known or mundane.

As our contribution to the effort to understand neural organization and functioning, we are developing computer-based methods for 3-D reconstruction, visualization and modeling of biological neural tissue. Experimental results are employed to fine tune the models. For our research, we use mammalian gravity sensing endorgans (maculas) as a prototype of more advanced systems. These sensors, like the rest of the nervous system, are morphologically organized for parallel processing of information (Ross et al., 1990b). There are two main intrinsic circuits and two neural inputs of extrinsic origin. In this report, we describe our computer-based methods for visualizing and simulating the intrinsic circuitry based on ultrastructural knowledge of macular architecture. We also describe the results of imaging this same neural circuitry in virtual reality, and discuss the potential of this type of visualization for future neuroscientific research.

### 3-D RECONSTRUCTION

A necessary first step in this research effort is development of an entirely automated method for 3-D reconstruction from sections studied in a transmission electron microscope (TEM). Reconstruction from TEM sections, although essential for precise knowledge of connectivities, is not widely practiced because of difficulties inherent to ultrastructural research. These are shrinkage during fixation and dehydration, and distortions introduced by compression during sectioning or by thermal warping during

exposure to an electron beam. This makes alignment (registration) of sections difficult and raises questions about accuracy once warping problems are resolved. A further issue is the sheer number of sections that must be assembled for a reconstruction of even a single neuron. For our earlier reconstructions, which relied on conventional photography and much manual labor, we used as many as 575 serial sections but digitized only every fifth or second section. A complicated reconstruction consumes months of effort.

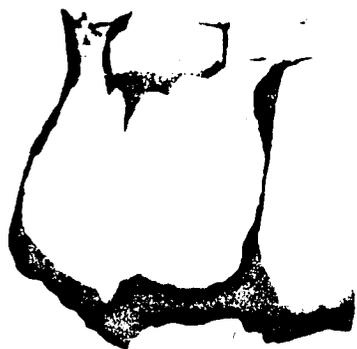


Figure 1. This semiautomated reconstruction is of a calyx (transparent) surrounding 3 hair cells with kinocilia (stick-like projections from hair cell heads).

Our current method (Montgomery and Ross, 1993) is semiautomated (Recon 2.0), eliminates tedious conventional photography, and enables use of every section (Figure 1). Two points are selected to bound the part of the section to be captured. A controlling computer then moves the TEM stage and micrographs are obtained with the use of a video or CCD camera. The images are sent via Ethernet to a Silicon Graphics (SGI) Indigo workstation in the computer laboratory of the Biocomputation Center. Adjacent images are reassembled (mosaicked) by a Connection Machine (CM5) to reproduce the sections. Contours of objects selected from the sections are traced, using the image displayed on a monitor. Tracing is aided by a zoom feature of the software. Contours of images are stacked in register using various algorithms. Individual contours can be expanded or shrunk if required because of tissue warping during preparation or data collection. Once images are registered, contours are connected by mesh generation (described below) and can then be visualized as shaded solids or as transparent objects if demonstration of inner structures is desired. Dimensions of the reconstructed image versus those recorded in the digitized micrographs are compared for accuracy, and shrinkage artifacts can be compensated for by the software.

Use of our reconstruction methods has resulted in new understanding of macular organization and circuitry. Macular receptive fields, defined as the distribution of type I and type

II hair cells (sensory cells of the macula) communicating with an afferent, overlap. No two receptive fields are identical. Moreover, individual hair cells comprising a receptive field do not have identical directional polarizations so that vector addition is involved in determining afferent output. The afferent of a type I cell is a complex ending (calyx) that is essentially a double-membraned sheet that wraps around the body(ies) of the type I cell(s). Calyces have slender, spine-like processes that end on type II cells pre- or postsynaptically or through recurrent connections. Additional processes of the afferent nerve fibers terminate on type II cells, and type II cells can be presynaptic to neighboring calyces. Thus, type I cells synapse only with their calyx, forming a highly channeled circuit; type II cells may synapse with several afferents, either pre- or postsynaptically, forming a distributed modifying circuit (Ross et al., 1991). These two intrinsic circuits are prototypic of the more advanced vertical and horizontal circuits of retina and olfactory bulb (Shepherd, 1970) and the direct and local circuits of cerebral cortex (Rakic, 1975; Schmitt, 1979). Better understanding of the prototypic architecture of maculas by computer-based reconstructions will be instrumental in achieving greater knowledge of the fundamental organization of neural tissue. This is essential for simulating neural activity on a grand scale.

A simple reconstruction of one nerve fiber ending and three small neurons, using Recon 2.0, required storage and manipulation of over a gigabyte of data. Expansion of the reconstruction to a cubic millimeter requires working with terabytes of data and teraflops of processing power.

### MESH GENERATION

The geometry of even very simple neural systems can be extremely complex, involving neurons having a tremendous variety of shapes and sizes, as well as complicated interconnections and branching. This structural heterogeneity provides a major challenge for the generation of surface meshes, which are needed both for visual representation of the three-dimensional structures and for the numerical simulation of the electrophysiology of nerve cells (see below). Automated detection of a branch as a separate object is a particularly difficult problem; but neurons often have hundreds to thousands of branches of various sizes.

An automated method has been developed that overcomes these difficulties and enables the generation of surface meshes over structures of any shape. The technique takes as input serial sections of a structure and derives a complete analytic description of its surface. This provides a basis for surface mesh generation of arbitrary resolution, which in turn may be used as a boundary definition to generate either quasi-two-dimensional or fully three-dimensional space-filling meshes.

The procedure can be summarized as follows. First, the interconnectivity of the serial sections is determined using a

simple overlap test as a heuristic. Stacks of interconnected contours are formed from this information. If a branch is detected, special "singular" contours are introduced that serve as a connection between different segments of the body.

Once the interconnectivity has been extracted, a fixed number of points are interpolated from the contours using a piecewise spline. The points on each contour are connected to corresponding points on adjacent contours in such a way as to minimize the "twist" of the surface between them. This then defines a uniform, two-dimensional network of points at which spatial locations on the surface of the structure are known. An analytic description of the surface is then derived from a tensor product (or related) interpolation between the points in the network.

The surface description thus obtained is used to generate quadrilateral or triangular surface elements that accurately retain the shape of the body. This may be done by simple interpolation, or through a more sophisticated incremental insertion technique. The resulting surface meshes can then be used to generate three-dimensional finite volume meshes in two ways. For structures such as a calyx, which consists of two parallel membranes separated by cytoplasm, a mesh one volume thick can be formed by interconnecting the inner and outer surface meshes. For more complex shapes, the surface meshes may be used as boundary definitions for tetrahedral or other mesh generators. The surface meshes generated improve our reconstructions and are employed directly in our biological simulations, described immediately below.

### BIOLOGICAL MODEL

The electrophysiology of neurons is sometimes modeled using a single partial differential equation for the transmembrane potential. This equation is:

$$\tau \frac{\partial \phi}{\partial t} = \lambda^2 \nabla^2 \phi - \phi$$

where  $\tau$  is the membrane time constant,  $t$  is time,  $\phi$  is the voltage displacement from rest,  $\lambda$  is the length constant, and  $\nabla^2$  is the Laplacian operator.

Traditionally, this equation has been solved by using a one-dimensional approximation of neural structures. However, a calyx in the macula is multi-dimensional, casting some doubt on the validity of this approximation (Jack et al., 1983). A more sophisticated approach is required, particularly for current spread at sites of juncture of branches and calyx. The problem of conserving charge at such sites, where one-dimensional and two-dimensional solvers must be integrated, is non-trivial. We have developed a novel, finite volume analysis approach that tracks the radial spread of current on a calyx membrane and has the

capability of transferring current between processes, modeled as 1-D cables, and calyces, modeled in 2- or 3-D.

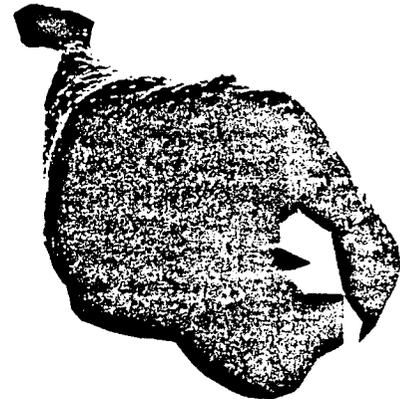


Figure 2. Radial spread of voltage (light areas, bottom right) from activation of synapses near the base of a calyx modeled using our finite volume method.

The numerical simulation code was written with the help of Tim Barth of the Fluid Dynamics Division, Algorithms and Applications Branch, at NASA Ames Research Center. The code uses a three-dimensional mesh which faithfully reproduces the shape of complex structures such as the calyx, while allowing one-dimensional treatment of long, thin processes. The algorithm is a fully implicit, finite volume technique that conserves charge. The volumes are defined by the perimeters of the polygons of the surface meshes. The linear system of equations that results at each timestep is solved using an iterative GMRES (Generalized Minimum Residual Solver).

In order to verify the accuracy of the algorithm, simulations were run of both one- and two-dimensional problems with analytic solutions. The agreement was excellent, indicating a faithful representation of the equations both in one and in multiple dimensions.

Because of the efficiency of the code, a fully functioning single calyx simulation can easily be run on a workstation. An independent graphical display interface has been written for SGI workstations. This allows interactive visualization of voltage change across the calyx over time. However, for more complex configurations, involving multiple interconnected structures, a supercomputer is required. For this reason, the code is now running on a Cray Y-MP C90.

Using these methods, we have learned that synaptic site is important in determining whether the voltage reaching the spike initiation zone is sufficient to discharge it. Voltage changes induced by synapse activation near the base of the calyx spread radially, as shown in Figure 2, so that a near maximal voltage is delivered to the nerve fiber

along which the spike initiator is located. The amount of voltage delivered to the calyx by a synapse on a process depends in part upon process morphology, and in part upon the voltage state of the calyx from moment to moment. This is because voltage changes proceed virtually unabated in the direction from calyx to process head, regardless of process morphology. For flow in this direction, processes act as voltage followers.

While the reconstruction and mesh generation methods have provided us with necessary tools for macular simulations, we believe the method has potential as a new, general purpose compartmental model. For this reason, the model is being tested in comparison with a 1-D compartmental model based on the program NEURON (Hines, 1989). We have already obtained results using NEURON and a wide range of morphometric data obtained from our reconstructions (Chimento et al., 1994). The new tests will begin to answer the question whether inclusion of minute details of dimensions and synapse locations, obtainable only through TEM serial section methods, and a strict, 3-D representation will yield different results from 1-D models in which compartments are collapsed.

#### CREATING A 3-D ABSTRACT NEURONAL NETWORK MODEL

The biological models discussed above rely heavily on reconstructions and details of the underlying macular morphology. Consequently, even the reconstruction of a small number of cells requires a great deal of computation. To simulate the function of the vestibular periphery, there must necessarily be less detail in the structure of individual components. Thus, the development of a functional model requires an abstraction from the level of morphological detail used in the mesh reconstructions while preserving constituent components. To this end we are developing an interactive 3-D abstract neuronal network representation of the vestibular periphery. This is based on a simple 2-D model that we had previously developed (Ross, et al, 1990a) and refined but includes the ability to interactively rotate, translate and scale the graphical representation.

In the present 2-D model, the anatomical structures are graphically depicted by simple geometric objects, circles and rectangles that reduce their drawing and updating complexity. The reduction in the complexity of the components allows a concomitant increase in the complexity of the system with, potentially, no added computational cost.

Use of our 2-D model has already led to interesting observations. One of the earliest of these was that inhibition was essential to include or else the simulation quickly saturated. Another was that, regardless of weighting, certain afferents could not be made to discharge in irregular patterns known to occur experimentally. We then included feedback and feedforward processes based on knowledge of their origins and terminations obtained from our reconstructions.

When these processes were included, the discharge patterns became more typical of the afferents simulated. This result was present under a variety of weightings. The findings have convinced us that inclusion of connectivities in three-dimensions may yield results that cannot be anticipated based on two-dimensional models.

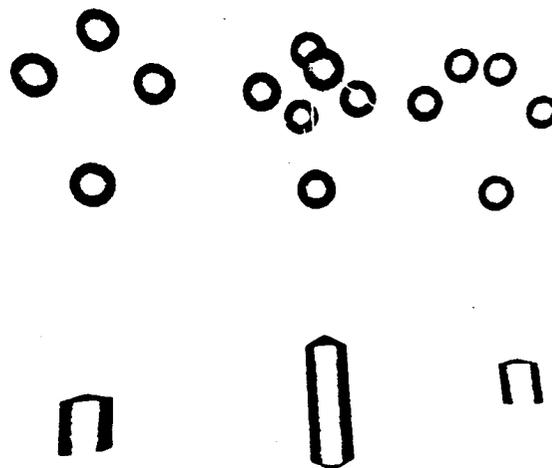


Figure 3. The 3-D abstract model comprises spheres to represent type I and type II hair cells (top two layers) and calyces (third layer), and cylinders to represent spike initiation zones (fourth layer). Lines are used to indicate functional as well as anatomical connections.

The 3-D abstract model we are developing uses the same individual complexity reduction/system complexity expansion technique employed in our 2-D model. The graphics library (GL) uses the hardware in the Silicon Graphics Personal Iris to allow objects to be drawn quickly. The model comprises representations for hair cells, calyces, spike initiation zones, afferent axons and the connections between these various structures (Figure 3). This latter category includes direct and lateral connections from hair cells to calyces, feedforward connections from the hair cells directly to the afferent axons and feedback connections from the calyces to the hair cells. The structure of this model, in terms of components and connections, reflects the anatomical considerations revealed in our electron microscope reconstruction studies. By choosing parameters derived from the more detailed biological simulation we hope that this model will capture the essential functional features of the vestibular periphery.

The next step in building the abstract model is to incorporate the physiological characteristics of the real system. In the 2-D model this was done quite simply, in a manner reminiscent of Artificial Neural Networks. Inputs from the various sensory structures are summed and passed through a sigmoid nonlinearity to produce an output. This formulation is presently included in the 3-D model for simplicity in development. The physiological characteristics of the model will be improved by including physiologically

more realistic neural paradigms based on a computationally efficient representation for spike initiation (Parnas and Lewis, 1993; Parnas, in review). This model will allow more complex response characteristics to be simulated. Input to the system represents a simulation of the relative motion of the otoconia and the hair cells, the magnitude of the input being based on the vector orientation of the sensory cells with respect to the motion of the otoconia. The hair cell responses are sent (via weighted connections) to the calyces with the appropriate lateral and feedback signals included. These responses, in turn, are sent along with feedforward signals to the spike initiators. Here the inputs are summed and a decision is made about the output status of the spike initiator (spiking versus not spiking). When large numbers of elements and interconnections are included we hope that the responses of the spike initiator array will be a faithful representation of the response of a portion of the peripheral vestibular system. With this many elements, the requirements for computation of the physiological response characteristics as well as for graphical display of a fully-interactive, symbolic representation of the system demand the computational power of supercomputers.

### VIRTUAL REALITY APPLICATIONS

Very rich data applications benefit from virtual environments because the combination of the three-dimensional display and control allow the user to intuitively explore the environment. For example, hand tracking allows the user to cause data to be displayed selectively, thus permitting the exploration of a complex data set.

The fully integrated virtual reality (VR) system combines parallel computer hardware, stereo visual display, 3-D audio displays, and a distributed software environment. We used an integrated virtual reality system combining the boom-mounted display and glove hardware that is located in the Numerical Aerodynamic Simulation Facility (NAS). We used our own reconstruction software and the VR library (developed at NAS) for the first stage of development of our VR Neuroscience application. For this first stage, we have successfully displayed 5 different data sets that include as many as 13 hair cells, 5 calyces and 4 nerve fibers, and branched as well as unbranched afferents.

Virtual reality will provide neuroscientists with a powerful tool that can aid in both the understanding of neural organization and functioning, and in the efficient analysis of the simulation model. One of our primary goals is to distribute the computation of the electrophysiological findings to a supercomputer over high-speed networks. This architecture has a variety of advantages, including higher computational speed so that more of the detailed, resource-consuming data can be visualized, and larger physical memory and higher disk bandwidth. Another interesting direction is to integrate auditory representation of the responsive virtual world. Examples would be sounds for ion channel opening and synaptic potentials, and a sound that

matches the frequency of discharge. The integration of the various parts of a virtual environment system into a coherent working whole is the most challenging and difficult aspect of virtual environment development.



Figure 4. This figure illustrates a reconstruction of a small part of the macular neuronal circuitry visualized in a virtual environment.

### SUMMARY AND CONCLUSIONS

The previous sections describe the computer-based methods we have developed to study the organization and functioning of the macular neural circuitry. We begin with serial sections studied in a TEM and proceed from 3-D reconstructions to computer simulations and visualization in a virtual environment. The focus is on a progression from understanding the unit structure to knowledge of how a collection of units are organized in three dimensions to achieve an appropriate physiological response. Including temporal features brings into play the fourth dimension of time. This progression, to be successful, requires the use of a variety of computational resources. High performance graphics workstations are more appropriate for development of the approaches while supercomputer power is required for automation of reconstruction and for scaling up simulations to large collections of neurons interacting over time.

Our results and those of other investigators strongly suggest that there is a fundamental neural architecture and that it basically conforms to a dual circuit system. That is, there are inputs that feed into the output neurons directly but there is another circuit that is always invoked. This second circuit consists of locally distributed neurons that distribute their output and modify the final information sent to another station. In its simplest form, the connections into the second circuit are made very locally by processes of the output neuron, as described for the vestibular macula. In a slightly more advanced variation, a single layer of interneurons is introduced at major levels of communication, as occurs in the retina. In still more advanced systems, such

as cortex, several different kinds of local cells and more layers of connections evolve. Nevertheless, the fundamental organization into two circuits remains. This has prompted Douglas and Martin (1992) to suggest that such dual circuitry is a canonical feature of neural tissue.

It seems likely that the first step in understanding the organization of interconnections between parts of the nervous system is to understand information processing by the circuits in their simplest versions in vestibular macula, retina and olfactory bulb. This is because interconnections between different levels of the central nervous system also mimic this architecture. Long axons feed into the dual circuits of distant neuronal tissues and receive a return input. This circuitry, known for some time, has been called a reentrant system by Edelman (1978).

The challenge before us is to understand some small part of the nervous system in its entirety, and to build upon that foundation. We believe that our computer simulations, based on real morphology and physiology, will be valuable as a stepping stone to the study of more complex systems and will provide a basis for increased understanding of memory, learning, creativity and consciousness.

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